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(54) Title: DEVICE FOR IN VIVO DELIVERY OF BIOACTIVE AGENTS AND METHOD OF MANUFACTURE THEREOF

(57) Abstract: The present invention consists of an implantable structural element for *in vivo* delivery of bioactive active agents to a situs in a body. The implantable structural element may be configured as an implantable prosthesis, such as an endoluminal stent, cardiac valve, osteal implant or the like, which serves a dual function of being prosthetic and a carrier for a bioactive agent. Alternatively, the implantable structural element may simply be an implantable article that serves the single function of acting as a time-release carrier for the bioactive agent.

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growth factor (FGF) gene transfers which have improved blood flow and collateral development in ischemic limb and myocardium (S. Yla-Herttuala, *Cardiovascular Gene Therapy*, Lancet, Jan 15, 2000), surgical intervention to remove the blockage, replacement of the blocked segment with a new segment of endogenous or exogenous graft tissue, or the use of a catheter-mounted device such as a balloon catheter to dilate the body lumen or an artherectomy catheter to remove occlusive material. The dilation of a blood vessel with a balloon catheter is called percutaneous transluminal angioplasty. During angioplasty, a balloon catheter in a deflated state is inserted within an occluded segment of a blood vessel and is inflated and deflated a number of times to expand the vessel. Due to the inflation of the balloon catheter, the plaque formed on the vessel walls cracks and the vessel expands to allow increased blood flow through the vessel.

In approximately sixty percent of angioplasty cases, the blood vessel remains patent. However, the restenosis rate of approximately forty percent is unacceptably high. Endoluminal stents of a wide variety of materials, properties and configurations have been used post-angioplasty in order to prevent restenosis and loss of patency in the vessel.

While the use of endoluminal stents has successfully decreased the rate of restenosis in angioplasty patients, it has been found that a significant restenosis rate continues to exist even with the use of endoluminal stents. It is generally believed that the post-stenting restenosis rate is due, in major part, to a failure of the endothelial layer to regrow over the stent and the incidence of smooth muscle cell-related neointimal growth on the luminal surfaces of the stent. Injury to the endothelium, the natural nonthrombogenic lining of the arterial lumen, is a significant factor contributing to restenosis at the situs of a stent. Endothelial loss exposes thrombogenic arterial wall proteins, which, along with the generally thrombogenic nature of many prosthetic materials, such as stainless steel, titanium, tantalum, Nitinol, etc. customarily used in manufacturing stents, initiates platelet deposition and activation of the coagulation cascade, which results in thrombus formation, ranging from partial covering of the luminal surface of the stent to an occlusive thrombus. Additionally, endothelial loss at the site of the stent has been implicated in the development of neointimal hyperplasia at the stent situs. Accordingly, rapid re-endothelialization of the arterial wall with concomitant endothelialization of the body fluid or blood contacting surfaces of the implanted device is considered critical for maintaining vasculature patency and preventing low-flow thrombosis. To prevent restenosis and thrombosis in the area where angioplasty has been performed, anti-thrombosis agents and other biologically active agents can be employed.

Summary of the Invention

As used herein the term "bioactive agent" is intended to include one or more pharmacologically active compounds which may be in combination with pharmaceutically acceptable carriers and, optionally, additional ingredients such as antioxidants, stabilizing agents, permeation enhancers, and the like. Examples of bioactive agents which may be used in the present invention include but are not limited to hydrophilic agents, hydrophilic agents, antiviral drugs, antibiotic drugs, steroids, fibronectin, anti-clotting drugs, anti-platelet function drugs, drugs which prevent smooth muscle cell growth on inner surface wall of vessel, heparin, heparin fragments, aspirin, coumadin, tissue plasminogen activator (TPA), urokinase, hirudin, streptokinase, antiproliferatives (methotrexate, cisplatin, fluorouracil, Adriamycin), antioxidants (ascorbic acid, beta carotene, vitamin E), antimetabolites, thromboxane inhibitors, non-steroidal and steroidal anti-inflammatory drugs, immunosuppresents, such as rapomycin, beta and calcium channel blockers, genetic materials including DNA and RNA fragments, complete expression genes, antibodies, lymphokines, growth factors (vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF)), prostaglandins, leukotrienes, laminin, elastin, collagen, nitric oxide (NO) and integrins.

The inventive structural material has a three dimensional conformation having a geometry and construction in which there is an internal cavity or a plurality of internal cavities within the structural material and a conduit or opening or plurality of conduits or openings which communicate between the internal cavity and external the structural material. The three dimensional conformation of the structural material may assume a cylindrical, tubular, planar, spherical, curvilinear or other general shape which is desired and suited for a particular implant application. For example, in accordance with the present invention there is provided an endoluminal stent that is made of a plurality of structural members that define a generally tubular shape for the endoluminal stent. At least some of the plurality of structural members are comprised of the inventive structural material and have at least one internal cavity and at least one conduit or opening which communicates between the internal cavity and external the stent. Alternate types of implantable devices contemplated by the present invention include, without limitation, stent-grafts, grafts, heart valves, venous valves, filters, occlusion devices, catheters, osteal implants, implantable contraceptives, implantable anti-tumor pellets or rods, or other implantable medical devices.

The inventive stent for delivery of bioactive agents consists generally of a plurality of structural elements, at least some of which have internal cavities that retain the bioactive

Figure 12 is a photomicrographic cross-sectional view taken along line 12-12 of Figure 11.

Figures 13A-13F are sequential diagrams illustrating the inventive method for fabricating the inventive endoluminal stent.

Figure 14 is are side-by-side photomicrographs illustrating selective formation of an internal cavity within the inventive endoluminal stent.

Detailed Description of the Preferred Embodiments

As noted above, the term "bioactive agent" is intended to encompass one or more pharmacologically active compounds which may be in combination with pharmaceutically acceptable carriers and, optionally, additional ingredients such as antioxidants, stabilizing agents, permeation enhancers, and the like. Examples of bioactive agents which may be used in the present invention include but are not limited to antibiotic drugs, antiviral drugs, neoplastic agents, steroids, fibronectin, anti-clotting drugs, anti-platelet function drugs, drugs which prevent smooth muscle cell growth on inner surface wall of vessel, heparin, heparin fragments, aspirin, coumadin, tissue plasminogen activator (TPA), urokinase, hirudin, streptokinase, antiproliferatives (methotrexate, cisplatin, fluorouracil, Adriamycin), antioxidants (ascorbic acid, beta carotene, vitamin E), antimetabolites, thromboxane inhibitors, non-steroidal and steroidal anti-inflammatory drugs, immunosuppresents, such as rapomycin, beta and calcium channel blockers, genetic materials including DNA and RNA fragments, complete expression genes, antibodies, lymphokines, growth factors (vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF)), prostaglandins, leukotrienes, laminin, elastin, collagen, nitric oxide (NO), and integrins.

With particular reference to Figure 1, the present invention consists generally of a body element 10 having a three-dimensional conformation defining X, Y and Z-axes of the body element 10 and at least one of a plurality of interior cavities 12 defined within the body element 10, and at least one of a plurality of passages or pores 14 which communicate between the at least one of a plurality of interior cavities 12 and exterior to the body element 10. While the body element 10 depicted in Figure 1 is of a generally cylindrical three dimensional conformation, alternative three dimensional conformations, such as planar, spherical, ovular, tetrahedral, curvilinear or virtually any other three dimensional conformation suitable for implantation into a living body is contemplated by the present invention. The plurality of passages 14 have dimensions sufficient to permit the bioactive agent to elute by diffusion, osmotic pressure or under the influence of a positive pressure applied by cellular in-growth into the plurality of interior cavities 12.

body 20. A first bioactive agent may be loaded into the first and third grouping of a plurality of internal cavities 12, while a second bioactive agent may be loaded into the second grouping of a plurality of internal cavities 12. Where, for example, the tubular body 20 is an endoluminal stent, stent-graft or graft which is implanted post-angioplasty, the proximal and distal ends of the tubular body 20 are anchored adjacent to healthy tissue while the intermediate region of the tubular body 20 are positioned adjacent to the diseased or injured tissue. In this configuration, a first bioactive agent, such as an endothelial growth factor and/or contrast medium to impart enhanced radioopacity to the tubular body 20 may be carried in the first and third groups of a plurality of internal cavities 12 and associated pores 14, while an anticoagulant, such as heparin, may be carried in the second group of a plurality of internal cavities 12 and associated pores 14. In this manner, the tubular body has enhanced radioopacity to aid in delivery and deployment and endothelial growth factors to enhance endothelialization of the tubular body 20, while delivering an anticoagulant directly to the site of the tissue lesion.

Moreover, where the internal cavities 12 are discontinuous, the plurality of pores 14 may be configured to include degradable plugs which degrade at different rates to expose different bioactive agents in the internal cavities 12 to the body at different points in time. Alternatively or additionally, the degradable plugs may degrade at different to expose the same bioactive agent in different internal cavities 12 at different periods of time to effectively elongate the period of time during which the bioactive agent is delivered. Alternatively, the plurality of pores 14 may be dimensioned to permit different elution rates of the bioactive agent and provide for a more protracted or time-release of the bioactive agent from the internal cavities 12. Moreover, by adjusting the carriers of the bioactive agent, *e.g.*, to provide more or less capacity to elute *in vivo*, in combination with alternate dimensions and orientations of the plurality of pores 14, *e.g.*, luminal or abluminally oriented, both the time of elution and the duration of elution may be adjusted.

The body element 10 is preferably formed of a metal such as titanium, vanadium, aluminum, nickel, tantalum, zirconium, chromium, silver, gold, silicon, magnesium, niobium, scandium, platinum, cobalt, palladium, manganese, molybdenum and alloys thereof, such as zirconium-titanium-tantalum alloys, nitinol, or stainless steel.

Turning to Figures 5-7 there is illustrated an alternative embodiment of the inventive endoluminal stent fabricated from a plurality of tubular structural elements 31 formed into a tubular stent and having a desired geometry. It will be appreciated that the generally hexagonal cell geometric pattern illustrated in Figure 5 is merely exemplary and a myriad of

42 having a three-dimensional conformation extending in the X-axis, Y-axis and Z-axis dimensionally. While the illustrated embodiment of the structural body 42 is planar, those of ordinary skill in the medical device fabrication art will understand that it is within the skill of the artisan to fabricate the structural body 42 of any desired three-dimensional conformation depending upon the desired use and indication of the implantable device 40. The three-dimensional conformation of the structural body 42 may be cylindrical, tubular, quadrilinear, planar, spherical, ovular, tetrahedral, curvilinear or virtually any other three-dimensional conformation suitable for implantation into a living body.

Like the above-described embodiments, the structural body 42 has at least one of a plurality of internal cavities 47, each of which carry a bioactive agent 47, and a plurality of openings 44 which pass from at least one upper 46, lower 48 or lateral 45 surface of the structural body 42, through the Z-axis thickness of the body and communicate with the at least one of a plurality of internal cavities 47 in the structural body 42. Where a plurality of internal cavities 47 are provided within the structural body 42, a plurality of bioactive agents 49 may be loaded into the structural body 42 with one or more bioactive agents 49 being loaded into each of the plurality of internal cavities 47.

Each of the above-described preferred embodiments of the present invention may be fabricated by a number of methods. In accordance with present invention, it is contemplated that either forming wrought metal parts, such as capillary tubing, into the implantable device or forming the implantable devices by vacuum deposition techniques are the preferred method of making the implantable structural elements of the present invention. Where an implantable device is to be fabricated of a plurality of individual tubular elements, such as depicted in Figures 5-7, pre-existing microtubular members having an outer diameter, for example, between 60 and 400 m and a wall thickness of between 10 and 350 m, may be employed to fabricate extremely small dimensioned devices suitable for intracranial or coronary artery applications. The microtubular members may be formed into a cylindrical endoluminal device, such as by braiding or bending and joining microtubular members together by spot welding. Where ends of the microtubular members are formed to be self-cannulating, the self-cannulating ends may be exposed on the abluminal surface of an endoluminal device at any point along the longitudinal axis thereof. The plurality of openings passing through the wall of each of the individual tubular elements may be formed by microdrilling the openings through the wall and into the internal cavity or lumen of the individual tubular members. The plurality of openings may be laser cut, etched or formed by EDM methods, and may be formed either pre- or post- formation of the tubular elements into

plurality of internal cavities 56 either to the blood stream, in the case of luminal micropores 58, and/or to adjacent tissue, in the case of abluminal micropores 58.

The at least one of a plurality of internal cavities 56 may be continuous or discontinuous throughout the inventive device 50. Specifically, in accordance with one preferred embodiment of the invention, the plurality of internal cavities 56 is discontinuous and each of the plurality of discontinuous internal cavities 56 reside within regions of the device 50 that are substantially non-load bearing regions of the device. In the particular embodiment illustrated in Figure 11, the plurality of hinge regions 54 are devoid of internal cavities 56 because they are load bearing regions of the stent. It is contemplated, however, that regions of the inventive device 50 that are deformed or that are load bearing may include either continuous internal cavities 56 or discontinuous internal cavities within their wall thickness and provide for elution of a bioactive agent retained within the internal cavity positioned at the load bearing region under the influence of a positive motivating pressure exerted on the bioactive agent by deformation or load stress transferred by the device geometry to the internal cavity and to the bioactive agent. By providing regions of continuous and discontinuous internal cavities 56, a plurality of bioactive agents may be loaded into different internal cavities 56 for achieving different elution rates and pharmacological effects. Figure 12 is a photomicrograph illustrating a transverse cross-sectional view through an individual structural element 52 illustrating the internal cavity 56.

Turning now to Figures 13A-F and 14 there is depicted a method for fabricating the inventive devices for delivery of bioactive agents. In Figure 13A a first layer 64 of a device-forming metal, such as titanium, vanadium, aluminum, nickel, tantalum, zirconium, chromium, silver, gold, silicon, magnesium, niobium, scandium, platinum, cobalt, palladium, manganese, molybdenum and alloys thereof, such as zirconium-titanium-tantalum alloys, nitinol, or stainless steel is formed onto a sacrificial substrate material 62. A sacrificial layer 66 is formed of a sacrificial material capable of being selectively removed without removing the underlying first layer 64. The next step involves selective removal of portions of the sacrificial layer 66 to leave cavity-forming portions 68 of the first sacrificial layer 66. A second layer 70 of a device forming metal, such as those enumerated above, is then formed onto the first layer 62 of the device forming metal and covers the cavity-forming portions 68. In the next step, depicted in Figure 13D, the plurality of micropores 72 are formed and pass through the second layer 70 and communicate with the cavity-forming portions 68. The plurality of micropores 72 may be formed by selective removal of the second layer 70 such as by laser or chemical etching. Alternatively, the second layer 70 of the device forming metal

the implantable device. Alternative, diffusion-mediated loading, osmotic loading or vacuum loading may be employed to load the bioactive agent into the internal cavities.

While the present invention has been described with reference to its preferred embodiments, those of ordinary skill in the art will understand and appreciate that variations in structural materials, bioactive agents, fabrication methods, device configuration or device indication and use may be made without departing from the invention, which is limited in scope only by the claims appended hereto.

growth factors, prostaglandins, leukotrienes, laminin, elastin, collagen, nitric oxide, and integrins.

5. An endoluminal stent, comprising:

a tubular member having a central lumen passing longitudinally through the tubular member and open at opposing ends of the tubular member, a luminal surface and an abluminal surface and a wall thickness defined therebetween, at least one internal cavity residing within the wall thickness in at least some portions of the tubular member, a plurality of openings communicating between the at least one internal cavity and at least one of the luminal surface, abluminal surface, proximal end or distal end of the tubular member, and at least one bioactive agent disposed in the at least one internal cavity.

6. The implantable body according to Claim 5, wherein the structural body further comprises a material selected from the group consisting of titanium, vanadium, aluminum, nickel, tantalum, zirconium, chromium, silver, gold, silicon, magnesium, niobium, scandium, platinum, cobalt, palladium, manganese, molybdenum and alloys thereof, such as zirconium-titanium-tantalum alloys, nitinol, and stainless steel.

7. The implantable body according to Claim 6, wherein the bioactive agent further comprises a pharmacologically active agent selected from the group of antibiotic drugs, antiviral drugs, neoplastic agents, steroids, fibronectin, anti-clotting drugs, anti-platelet function drugs, drugs which prevent smooth muscle cell growth on inner surface wall of vessel, heparin, heparin fragments, aspirin, coumadin, tissue plasminogen activator, urokinase, hirudin, streptokinase, antiproliferatives selected from the group of methotrexate, cisplatin, fluorouracil and adriamycin), antioxidants selected from the group of ascorbic acid, beta carotene and vitamin E, antimetabolites, thromboxane inhibitors, non-steroidal and steroidal anti-inflammatory drugs, immunosuppresents, such as rapomycin, beta and calcium channel blockers, genetic materials including DNA and RNA fragments, complete expression genes, antibodies, lymphokines, growth factors, vascular endothelial growth factor, fibroblast growth factor, prostaglandins, leukotrienes, laminin, elastin, collagen, nitric oxide, and integrins.

11. An endoluminal stent for delivering a bioactive agent to a situs in a body, comprising a plurality of structural elements interconnected to form a cylindrical member, each of the plurality of structural elements a the wall thickness further comprising a plurality of lamina positioned concentrically through the wall thickness and a plurality of tubular member having an exterior surface and an interior surface together defining a tubular member thickness of said tubular member, said tubular member having a recessed active agent receiving portion formed in said exterior surface, said recessed active agent receiving portion having a depth less than said tubular member thickness, said recessed active agent receiving portion containing at least one active agent.

12. The endoluminal stent according to Claim 11, wherein the endoluminal stent is fabricated by vapor deposition of at least one metal.

13. The implantable body according to Claim 12, wherein the at least one metal is selected the group consisting of titanium, vanadium, aluminum, nickel, tantalum, zirconium, chromium, silver, gold, silicon, magnesium, niobium, scandium, platinum, cobalt, palladium, manganese, molybdenum and alloys thereof, such as zirconium-titanium-tantalum alloys, nitinol, and stainless steel.

14. The implantable body according to Claim 11, wherein the bioactive agent further comprises a pharmacologically active agent selected from the group of antibiotic drugs, antiviral drugs, neoplastic agents, steroids, fibronectin, anti-clotting drugs, anti-platelet function drugs, drugs which prevent smooth muscle cell growth on inner surface wall of vessel, heparin, heparin fragments, aspirin, coumadin, tissue plasminogen activator, urokinase, hirudin, streptokinase, antiproliferatives, antioxidants, antimetabolites, thromboxane inhibitors, non-steroidal and steroidal anti-inflammatory drugs, immunosuppresents, such as rapomycin, beta and calcium channel blockers, genetic materials including DNA and RNA fragments, complete expression genes, antibodies, lymphokines, growth factors, prostaglandins, leukotrienes, laminin, elastin, collagen, nitric oxide (NO), and integrins.

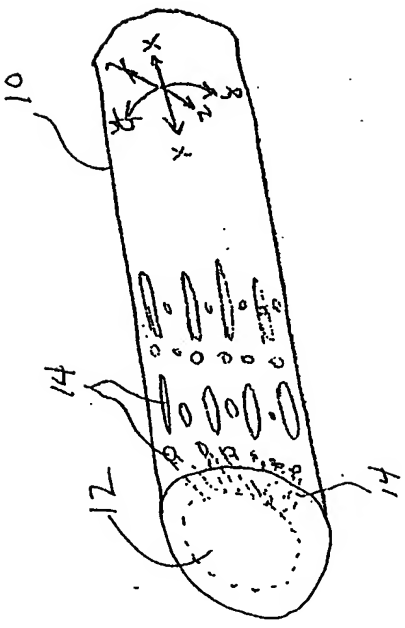

FIG 1

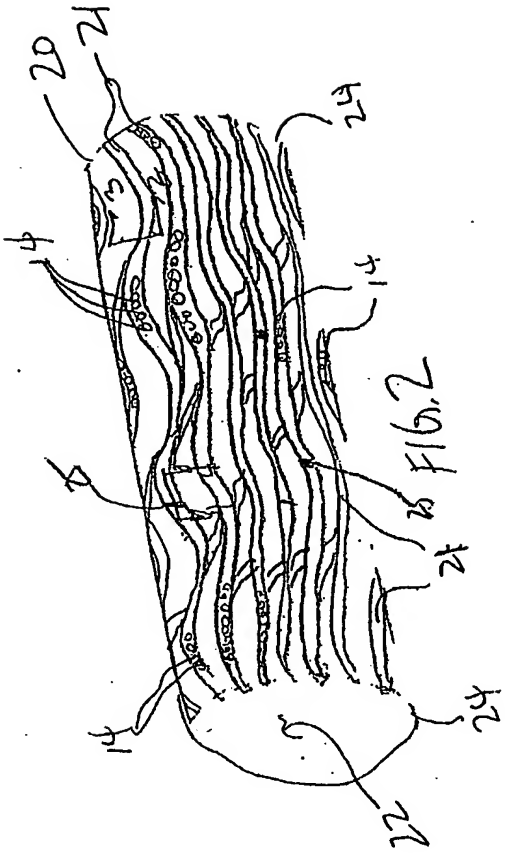

FIG 2

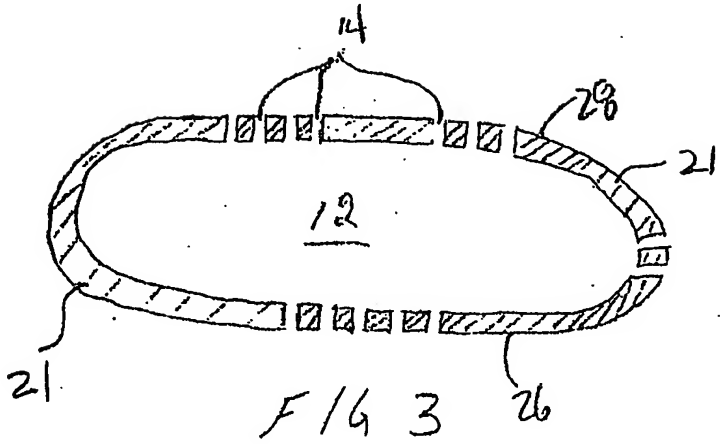

FIG 3

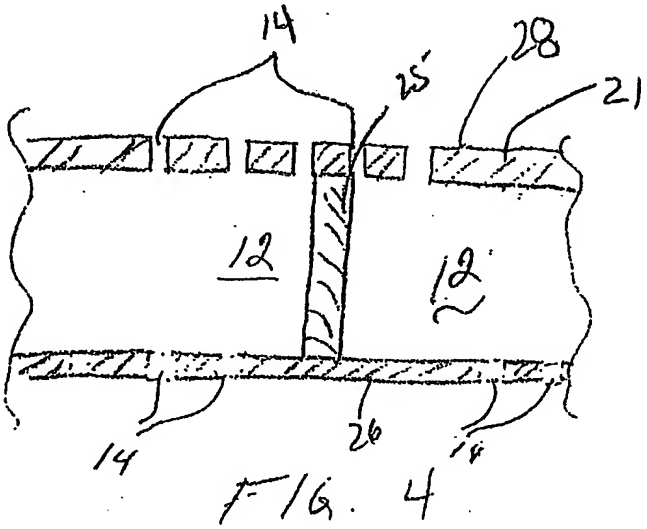

FIG. 4

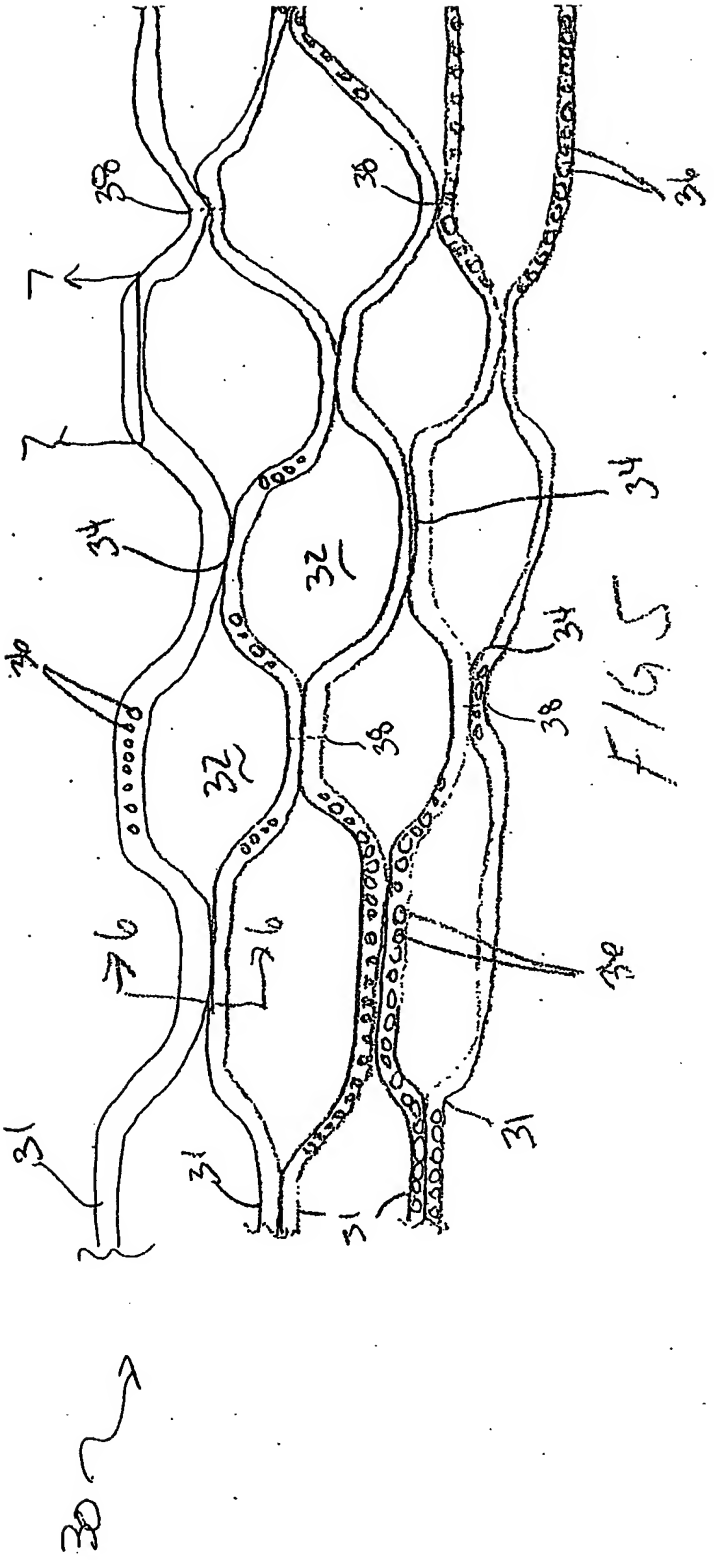

FIG 5

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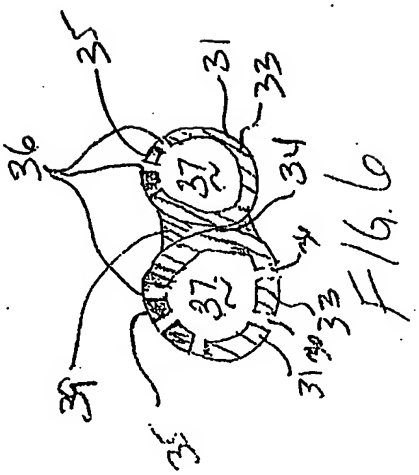

FIG. 6

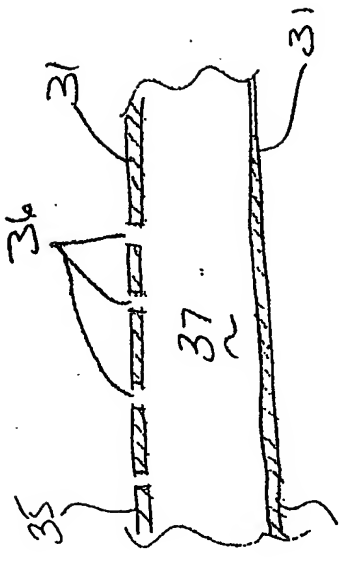

FIG. 7

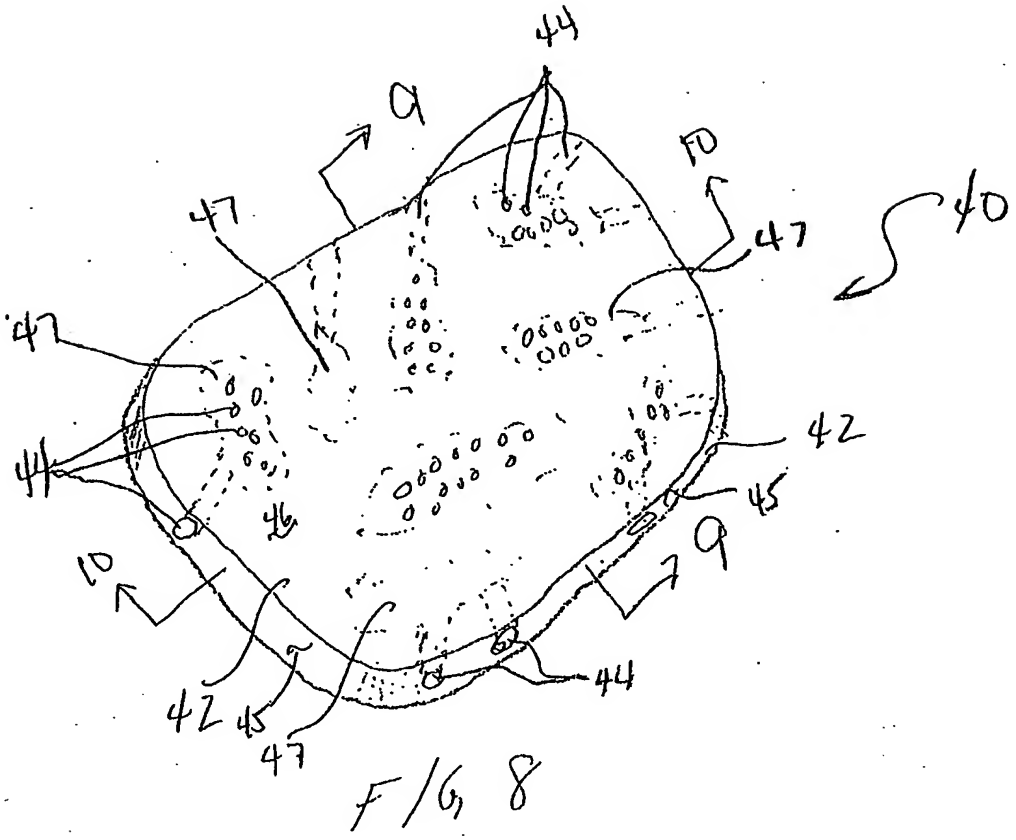

FIG 8

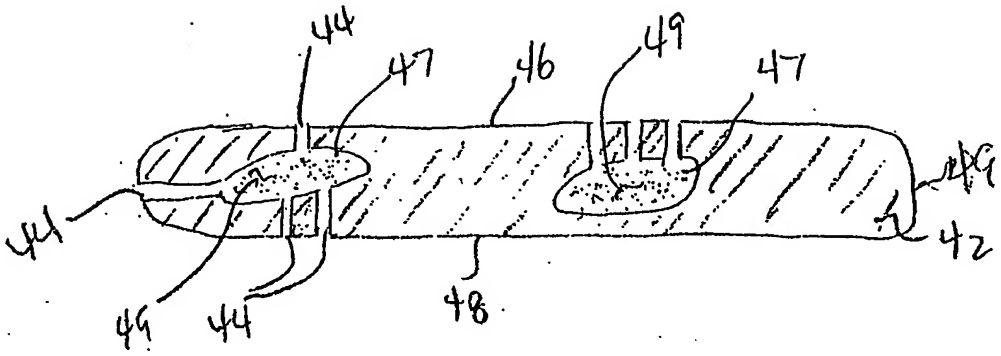

FIG. 9

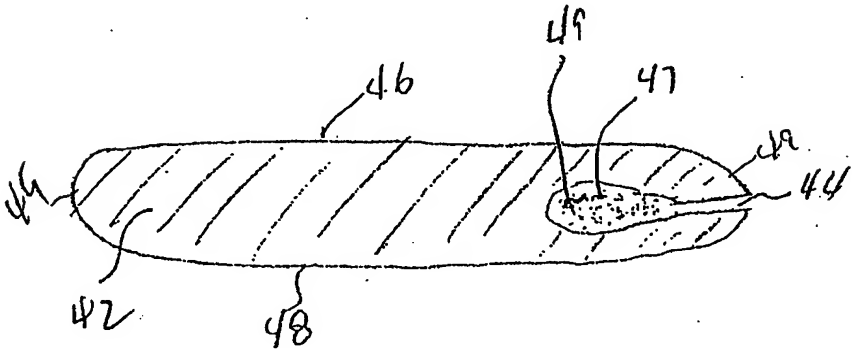

FIG 10

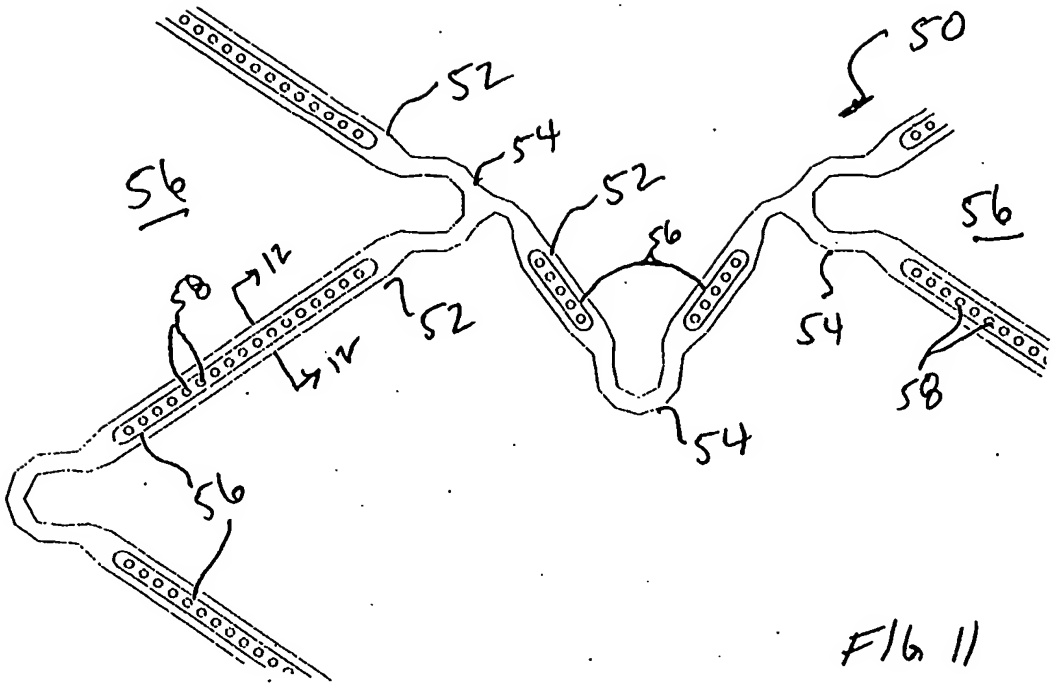

Fig 11

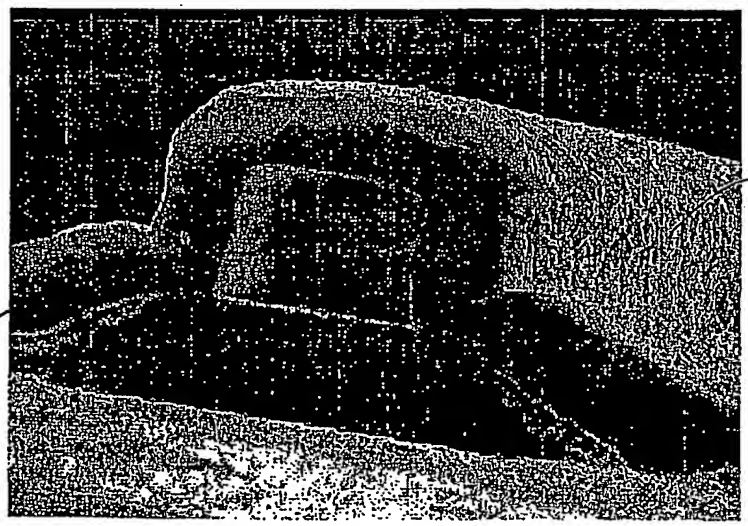

Fig 12

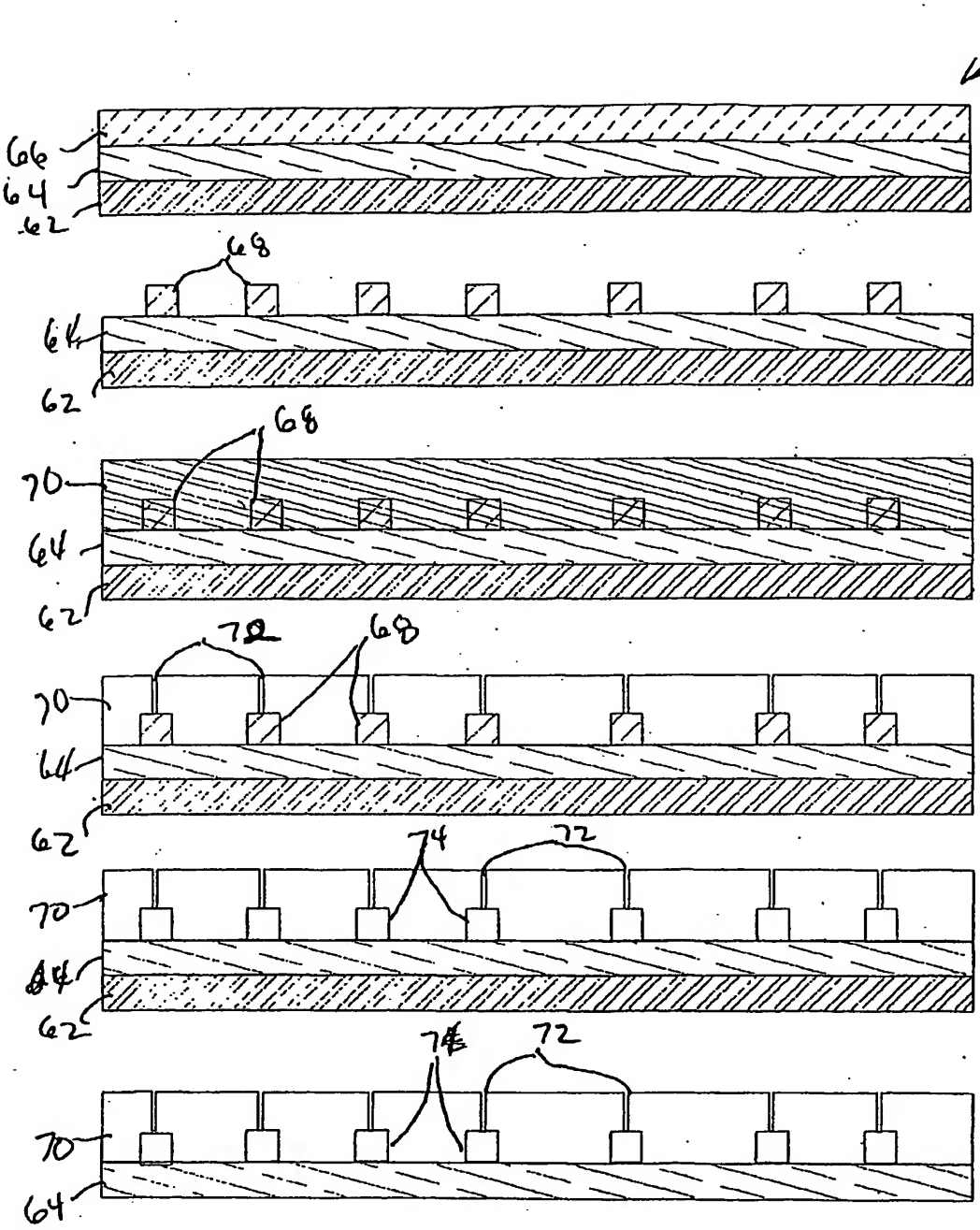

FIG 13A

FIG 13B

FIG 13C

FIG 13D

FIG 13E

FIG 13F

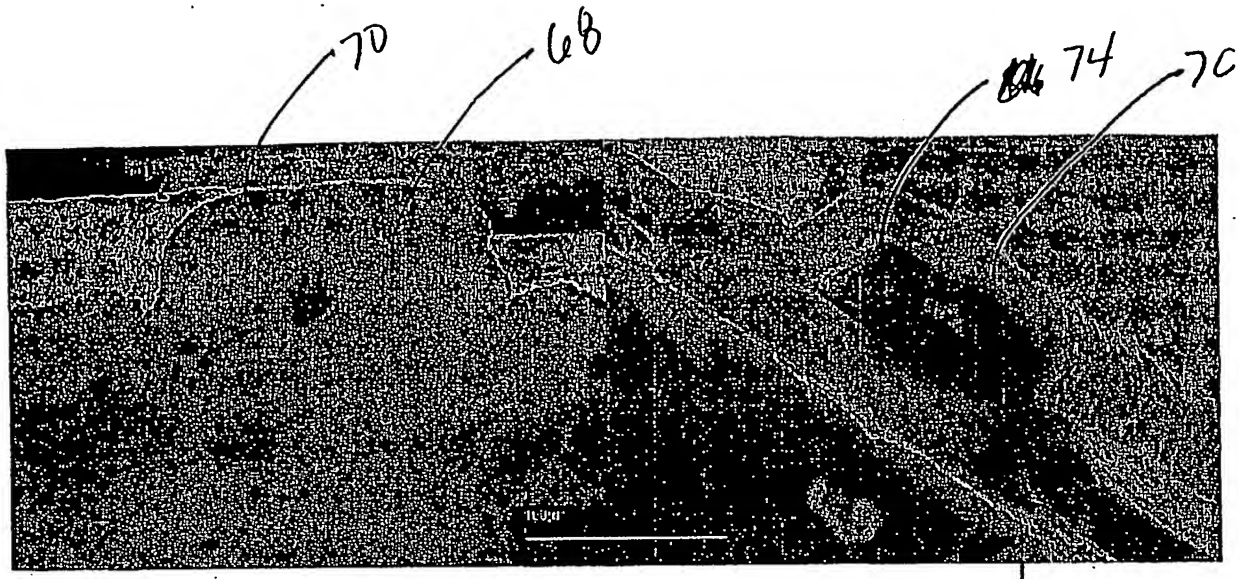

FIG 14